(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26591 A1

(51) International Patent Classification[7]: A61F 9/008

(21) International Application Number: PCT/US00/28446

(22) International Filing Date: 13 October 2000 (13.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/159,625	14 October 1999 (14.10.1999)	US
60/200,709	27 April 2000 (27.04.2000)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/159,625 (CIP)
Filed on	14 October 1999 (14.10.1999)
US	60/200,709 (CIP)
Filed on	27 April 2000 (27.04.2000)

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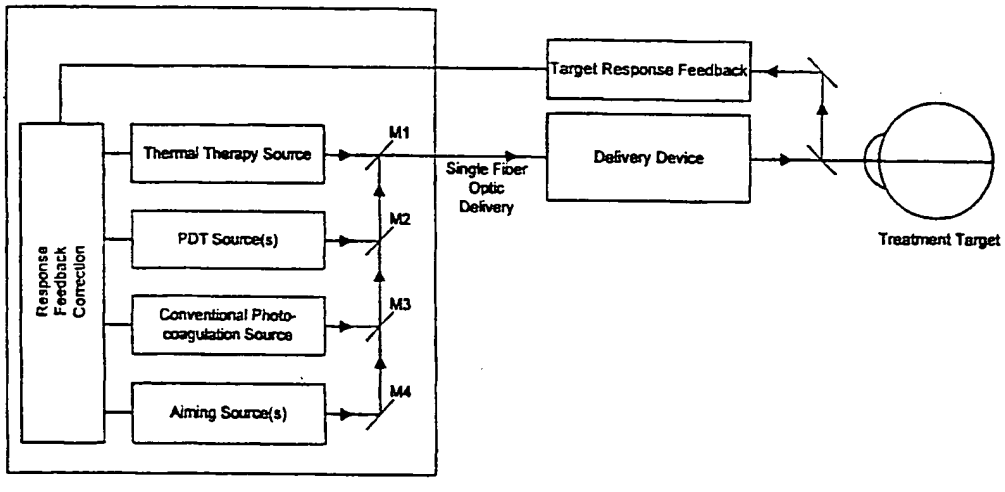
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

[Continued on next page]

(54) Title: THERAPEUTIC USE OF LONG-PULSE LASER PHOTOCOAGULATION IN COMBINATION WITH OTHER TREATMENT MODALITIES



Laser Beam Deflectors M1, M2, M3, M4 may be fixed or mobile

(57) Abstract: A method and apparatus are provided for treating a variety of disease states using thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long- pulse photocoagulation. These disease states include but are not limited to cancer, ocular neovascularization and abnormal vascular conditions throughout the human body.

WO 01/26591 A1

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

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THERAPEUTIC USE OF LONG-PULSE LASER PHOTOCOAGULATION IN COMBINATION WITH OTHER TREATMENT MODALITIES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a method and apparatus for treating disease states using feedback-controlled, long-pulse laser photocoagulation in combination with photodynamic therapy (PDT), exogenous chromophores, thermally activated molecules or compounds, or conventional short-pulse laser photocoagulation. Disease states for treatment include, but are not limited to, ocular neovascularization and abnormal vascular or neoplastic conditions throughout the human body.

Description of Related Art

Since the 1860s, hyperthermia has been studied as an anti-cancer modality. At that time, it was noted that facial sarcomas regressed after prolonged bouts of fever. The earliest human studies were performed on cutaneous tumors such as squamous cell and malignant melanomas. In ophthalmology, laser-induced hyperthermia is a low-irradiance, long-pulse photocoagulation procedure referred to as transpupillary thermotherapy or TTT. TTT was first described by Overgaard, et al. in 1987 when it was used as an adjunct to radiotherapy in the treatment of choroidal melanomas.

Hyperthermia may be defined as the elevation of tissue temperature above its normal temperature. If tissue suffers biological damage after exposure to a particular hyperthermic temperature for a certain period of time, the hyperthermic heat dose for that exposure is defined clinically as the time in

minutes that would be needed for a 43°C exposure to cause the same amount of damage. Reliable clinical hyperthermia requires accurate thermometry which can be performed with a variety of nonmetallic temperature-sensitive crystal and/or fiber-optic probes or by nuclear magnetic resonance.

Hyperthermia can be applied as either total body systemic hyperthermia or localized heating. Localized ophthalmic hyperthermia has the same difficulties as other forms of local therapy, which include maintaining the intended temperature elevation within tissue treatment areas, monitoring tissue responses accurately, and providing effective delivery systems for hyperthermia.

Laser-induced hyperthermia can be optimized by proper selection of laser wavelength, irradiance, pulse duration, spot size and pulse profile. Near-infrared radiation is currently used for TTT because of its relatively high penetration into pigmented tissue and low absorption by ocular media. Exposures of one minute or more with a beam diameter of several millimeters are typically used for near-infrared TTT with 810 nm diode laser radiation. Other wavelengths such as 1064 nm and visible wavelengths between 400 and 700 nm can produce different temperature distributions. Ultrasound, microwave and ferromagnetic thermoseeds are other potential energy sources for hyperthermia therapy.

Choroidal melanomas and retinoblastomas respond to transpupillary thermotherapy (TTT). Histologic studies of TTT-treated choroidal melanomas have shown extensive thrombosis of tumor vessels following treatment. This may be the mechanism by which TTT scleroses choroidal neovascularization (CNV) in age-related macular degeneration (ARMD). TTT may produce cicatrization of the CNV complex. This may limit subretinal exudation and macular edema, effectively reducing their damaging effects to the neurosensory retina and preserving visual acuity. However, all neovascular conditions do not appear to respond equally well to TTT. As an example, classic CNV may not respond as well to TTT as occult CNV.

PDT is a relatively new method for treating chorioretinal tumors and abnormal blood vessels (neovascularization). PDT involves topical or

intravenous delivery of a photosensitizing drug to target tissues and subsequent activation of the drug by incident laser radiation of an appropriate wavelength. The activated photosensitizer destroys target tissues by generating an active form of oxygen (singlet oxygen) resulting from transfer of the energy from the excited photosensitizer to endogenous oxygen. Proper selection of the type and dose of photosensitizer, post-infusion schedule of light application and light dose can result in destruction of a tumor or neovascularization with little or no damage to surrounding or overlying normal tissue. This treatment appears to be beneficial for certain patients with classic CNV. However, the effects seem to be temporary, with a high rate of CNV recurrence and a resultant high retreatment rate.

In conclusion, there is clearly a need for an improved method and apparatus for treating many disease states that are associated with the development of abnormal blood vessels or neovascular structures.

SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is to provide a method and apparatus for treating a variety of disease states.

Another object of the present invention is to provide a method and apparatus for treating abnormal blood vessels.

A further object of the present invention is to provide a method and apparatus for treating abnormal blood vessels using thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long-pulse photocoagulation. Long-pulse laser photocoagulation includes but is not limited to TTT.

Still another object of the present invention is to provide a method and apparatus for treating cancer, ocular neovascularization and abnormal vascular conditions throughout the human body using thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long-pulse photocoagulation.

Yet another object of the present invention is to provide a method and

apparatus for treating a variety of different disease states using thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long-pulse photocoagulation.

Still a further object of the present invention is to provide a method and apparatus for treating CNV.

Accordingly, the present invention provides a method and apparatus for treating a variety of disease states thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long-pulse photocoagulation.. These disease states include but are not limited to cancer, ocular neovascularization and abnormal vascular conditions throughout the human body.

These and other objects of the present invention are achieved in a method of creating a therapeutic change in a target tissue site. A first treatment modality is controllably delivered to the tissue treatment site. Subsequently, a second treatment modality is controllably delivered to the same lesion.

In another embodiment of the present invention, a treatment system includes first and second treatment modality sources. A tissue feedback control system is coupled to at least one of the first and second treatment modality sources. The tissue feedback control system provides an adjustment of a delivery of the first or second treatment modality to an tissue site in response to feedback received from the tissue site.

In another embodiment of the present invention, a method of treating age-related macular degeneration is provided. First and second treatment modalities are controllably delivered to an ocular treatment site

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic diagram of one embodiment of the present invention using one laser for producing the output for the thermotherapy modality and an additional laser for the PDT and/or conventional photocoagulation modality. Multiple sources share a common enclosure and/or certain power or control elements and address a single delivery device through a

common optical fiber.

Figure 2 is a schematic diagram of another embodiment of the laser system of the present invention in which multiple sources share a common enclosure and address a single delivery device through a plurality of optical fibers.

Figure 3 is a schematic diagram of another embodiment of the laser system of the present invention in which individual sources address a single delivery device through multiple optical fibers.

Figure 4 is a schematic diagram of another embodiment of the laser system of the present invention in which individual sources sequentially address a plurality of delivery devices through multiple optical fibers.

DETAILED DESCRIPTION

The present invention is a method and apparatus for treating abnormal blood vessels throughout the human body using thermal therapy in combination with PDT, and/or conventional short-pulse photocoagulation and/or long-pulse photocoagulation. More particularly, the present invention is a method and apparatus for closing off selected blood vessels. Embodiments of the present invention include, but are not limited to, the combinations of: (i) thermal therapy with PDT, (ii) thermal therapy with exogenous chromophores, (iii) thermal therapy with conventional short-pulse laser photocoagulation, (iv) thermal therapy with long-pulse laser photocoagulation, and (v) thermal therapy with thermally activated molecules.

One embodiment of the present invention is a method and apparatus that utilizes a multitude of different treatment modalities (TTT and PDT, as one example) for the treatment of abnormal blood vessels that develop in the body that may be caused by tumors, eye disorders, vascular disorders, and the like. The apparatus used to effect this multi-pronged treatment may be comprised separate or integrated treatment sources, and separate or integrated delivery devices. An example of an eye disorder that is treated by the present invention includes, but is not limited to, neovascularization from age-related macular

degeneration, diabetic retinopathy and ocular tumors.

In various embodiments, TTT and PDT (as an example of a combination treatment modality) are performed simultaneously, or TTT is performed first followed by PDT, or PDT is performed before application of TTT, or one of the modalities is initiated and then the other begins while the first one continues. The combination of TTT and PDT provides synergistic or additive enhancement of the two treatment modalities. Circular treatment spots are used most commonly, but annular or otherwise non-circular treatment spots may be employed to achieve more favorable temperature profiles in chorioretinal tissue. The intensity profile of the treatment spot may also be adjusted to provide a temperature profile with greater treatment efficacy.

PDT can be used to achieve a selective and temporary closure of abnormal blood vessels. When combined with TTT, these two treatments techniques enhance the treatment of abnormal blood vessels and can minimize deleterious side effects to surrounding structures. Any appropriate photosensitizer drugs can be utilized in the PDT treatment of the present invention. Suitable photosensitizer drugs may include, but are not limited to, tin ethyletiopurpurin ("SnET2"), activated at 664 nm and available from Miravant/Pharmacia, benzoporphyrin derivative ("Visudyne"), activated at 690 nm and available from QLT/Ciba Vision and NPE6 LUTEX ("lutetium texaphyrin"), activated at 732 nm and available from Pharmacyclics/ Alcon. Additional potential photosensitizer drugs are being investigated.

One embodiment of the present invention provides a laser system that delivers optical energy at a specific wavelength suitable for PDT, a second wavelength suitable for TTT and optionally one or more wavelengths for aiming the laser at the designated target. In another embodiment, a laser is provided for the delivery of optical energy for PDT applications, and a different energy source, including but not limited to RF, microwave, a resistive heater, ultrasound and the like, is used to deliver the energy for the thermal therapy application. The two energy sources may be controlled in such a way as to perform PDT alone, thermal therapy alone, or PDT and thermal therapy in any

sequence or combination, including single or multiple treatments. PDT and hyperthermia may be synergistic if PDT is delivered prior to, or at the same time as, hyperthermia, but may only be additive if hyperthermia is given first and damages the vasculature required for effective PDT oxygenation.

One embodiment of an apparatus of the present invention is a laser system 10 illustrated in Figure 1. System 10 includes a TTT laser 12 and at least one PDT laser 14. Optionally, additional lasers 16, 18, 20 and like, can be included in multiple wavelengths are desired. In one embodiment of system 10 of Figure 1, laser 14 is an 810 nm I.R. diode laser and laser 14 that emits a wavelength corresponding to a specific PDT drug's absorption peak. The output of system 10, with a single or two combined laser beams, is coupled by an optical fiber 20 to a suitable delivery device including but not limited to a bare fiber, a handpiece, an EndoProbe, an endoscope, a slit lamp, an indirect ophthalmoscope, an operating microscope, a scanning laser ophthalmoscope and the like. A control system contains a power supply with the functional and operating controls for all of the lasers 12 and 14, as well as optional lasers 16, 18, 20, as well as additional lasers. The control system allows the selection and programming of single or simultaneous or sequential delivery of optical energy to the selected tissue site. Additionally, the control system provides for the adjustment and display of individual laser operating parameters as well as offering a means for the optional synchronization of laser delivery with external drug infusion systems. Further, the control system can include means to measure the power delivered in each wavelength component of the combined beam and to adjust each laser output to obtain the desired result.

In another embodiment, illustrated in Figure 2, system 110 includes a first laser 112, a second laser 114 and an aiming laser 116. Included are a control amplifiers 118, 120 and 121, feedback correction devices 122, 124 and 126, and power sensors 128 and 130, coupled to lasers 112, 114 and 116. Feedback correction devices 122, 124 and 126 are coupled to a timing and command device 132 which is coupled to an operator display and control device 134. Power sensors 128 and 130 are each coupled to a beam selector/combiner

136 and 138, respectively. The outputs of lasers 112, 114 and 116 are delivered by a single optical fiber 140 that is coupled to a delivery device 142.

The embodiment illustrated in Figure 3 is similar to the embodiment of Figure 2 except that the output of laser 112 is coupled to a first optical fiber 144, and the outputs of lasers 114 and 116 are coupled to a second optical fiber 146.

The embodiment illustrated in Figure 4 is similar to the embodiment of Figure 3 except there are two timing and command devices 148 and 150 and two operator display and control devices 152 and 154. Operator display and control devices 152 and 154 communicate with each other. Additionally, a second aiming laser 156, with a feedback correction device 158 and a control amplifier 160, is associated with first laser 112.

A benefit of TTT may be that it causes apoptosis but minimizes accidental cell death. In the absence of any ophthalmosopically visible endpoint various means and treatment strategies may be implemented to titrate energy delivery appropriately for each patient. Such schemes may fall into, but are not limited to, the general categories of (i) predictive, (ii) real-time (or essentially so), or (iii) conformational measurements of TTT action.

Predictive measurements and treatment strategies attempt to measure the likely response of a specific target (e.g., a patient's retina) to TTT prior to its application. For example, the retinal reflectivity at or near the TTT wavelength, delivered at an attenuated, subtherapeutic power, may be measured and compared with values obtained from other patients' eyes, permitting an appropriate adjustment of the specific TTT parameters. Another potential predictor is the optical transmission through the eye at the TTT wavelength. Greater transmission implies lower chorioretinal absorption and thus a need to increase the TTT dose. A small light-sensing episcleral probe may be positioned directly posterior to the TTT target to facilitate this measurement. This probe may be disposable.

Another predictive strategy involves the application of one or more suprathreshold laser test burns. An algorithm developed theoretically, semi-empirically or experimentally then relates parameters used to produce these

visible burns to appropriate TTT parameters.

Real-time measurements are those signals occurring during the TTT treatment that change fast enough to be used to control the TTT parameters. Real-time measurements may monitor the temperature of the target tissue directly, or may measure a secondary response of the tissue that in turn is related to temperature.

Real-time temperature measurements may be achieved with a variety of hardware and methods that include, but are not limited to, the use of (i) an episcleral thermosensitive probe such as a thermocouple or thermistor element, (ii) transpupillary IR thermography, (iii) liposome encapsulated fluorophore, (iv) MRI, (v) ultrasound, (vi) retinal reflectometry, including signals collected by camera, video cameras and scanning laser ophthalmoscope-like (SLO) instruments, (vii) a thermally modulated fluorescent substance, (viii) focal or multifocal ERG, (ix) thermal imaging, (x) optical coherence tomography (OCT), (xi) multispectral imaging, (xii) fluorescent and autofluorescent signals and (xiii) retinal thickness changes as measured with retinal thickness analyzer apparatus.

Confirmational measurements and strategies are those techniques performed subsequent to TTT administration in order to confirm adequate treatment. In addition to all of the real-time signals cited previously that may also persist after the conclusion of TTT, other signals or conditions that are slower to develop may be monitored. These other signals of potential value include post-treatment fundus photography and angiography (both fluorescein and indocyanine green (ICG).

Examples of indicators for the secondary tissue response include, but are not limited to, (i) oxygen saturation in tissue or blood, (ii) blood vessel diameter, (iii) detection of response of some biological factor such as heat shock protein(s) [*HSP*], (iv) a change in cell size and (v) hemoglobin density.

Oxygen and thermal sensors can be used. Changes in the blood vessel are indicative of changes in the level of oxygen, and thus are used as a feedback tool to monitor changes in the target tissue. The same is true for monitoring

new vessel stimulation events. Changes in blood vessels are readily determined by detecting a signal that is representative of a change in blood vessel diameter such as detection of specular reflection.

Diffraction by the blood vessel is the inverse of diffraction by a single slit (i.e., Hertzhog diffraction). By reversibility the diffraction patterns are the same, and the width of the slit determines the spread of higher order diffraction modes and in particular, their width. Thus a change in blood vessel diameter is measured by a corresponding change in the diffraction pattern which can be measured, calibrated and correlated with a temperature change. The vascular response relative to the change in the blood vessel is detected by sensing an endpoint following subthreshold treatments. This can be achieved with a single wavelength or with a wavelength that penetrates the vessel and another that does not. Alternatively, the optical density of the light reflected from the blood vessel can be detected. A digital photograph of the vessel can be taken to ascertain if there have been changes. This can be achieved with the use of a scanning laser ophthalmoscope.

The principal objective of the temperature measurement system is to allow the doctor to deliver a controlled dose of energy to the patient so as to achieve the desired therapeutic effect. In essence, the apparatus is an energy dosimeter. As such, another embodiment of the invention employs two effects within the eye. During treatment a visible wavelength will vary in reflection as the retina elevates in temperature. This change may be measured and used to provide feedback to the delivery system. The reflection varies depending upon individual retinal structure, pigmentation, and a number of other competing factors.

Laser speckle measures surface roughness to within an angstrom or so. For retinal measurement laser speckle provides a measure of changes in the cell size, shape or structure which alters their surface quality. An example of a method and apparatus of a speckle measuring system is disclosed in U.S. Patent No. 5,763,789, incorporated herein by reference. Measurement of laser speckle involves detection of the periodic variation in reflected light intensity from the

scattering site. The spacing of the bright points which make up the "speckle" is dependent upon the roughness of the reflecting surface. A fixed light source emits a planar light beam, typically collimated laser radiation, that is directed at the specimen by two mirrors mounted to jaws and on one side of the specimen. One of these mirrors is secured to, and moves with, the moving jaw and directs the light beam toward the specimen along a transverse path; the other mirror is mounted to the fixed jaw. A fixed light receiver receives the light beam after it has passed over the specimen and has been reflected by a similar pair of mirrors mounted to the jaws but on the other side of the specimen. Changes in the positional profile of the light beam caused by specimen deformation are detected by the receiver and converted into physical measurements of deformation and deformation rate.

Multi-wavelength measurements can be used to sense and control temperature during the treatment phase of TTT.

Changes in the optical density of ocular pigments could be used as an indirect measure of the thermal dose of long pulse PC. Such pigments could include, but are not limited to, rhodopsin, xanthophyll, hemoglobin, oxyhemoglobin and melanin.

For example, the extinction coefficients of oxygenated and reduced hemoglobin are nearly equal at 800 nm and are quite different at 650 nm. Reflections at these two, or other similarly related, wavelengths may be used together to measure changes in blood oxygen levels caused by temperature elevation.

With absorption, light in the red/near-IR penetrates the tissue, giving scatter and diffraction off retinal vessel. If the vessels change diameter, for example when heated, this change can be measured very accurately by the change in diffraction by the vessels, similar to a slit causing a diffraction pattern.

Polarimetry is also a useful method to sense and control for purposes of monitoring changes in tissue. During polarimetry, the reflection of polarized light is detected and analyzed. Certain vessels preserve the polarization; others

scramble it. The degree of scrambling is temperature dependent and can be measured using a polarized light source and a polarization sensitive detector.

An example of a method and apparatus of a polarization measuring system is disclosed in U.S. Patent No 6,027,216: Eye fixation monitor and tracker. Apparatus and method are provided for assessing the direction of fixation of an eye by detecting polarization-related changes in light retroreflected from the fundus of the eye. Nerve fibers in the retina of the eye are birefringent and alter the polarization state of light traversing them as a function of their orientation. The nerve fibers are arrayed in a characteristic pattern in the retina, specifically radiating outward from the fovea and converging to the optic nerve head. By assessment of polarization-related changes in retroreflected light from multiple retinal areas either sequentially or simultaneously, characteristic birefringence signatures of portions of the retina can be identified which are used to assess the direction of fixation of the eye.

Another method for sensing and controlling temperature during the treatment phase of TTT is wavefront measurement. The wavefront of a light beam gives two metrics. The first metric is for any physical change on the treatment area, including but not limited to thermal expansion, change in cellular spacing or shape, and the like. Examples of suitable probe resolution capabilities are 0.1 um if probing in the red (at wavelengths around 670 nm) or 0.05 um in the blue (at wavelengths around 500 nm). The second metric is a change in refractive index due to heating. This metric can be used to resolve temperature changes of a few degrees centigrade.

Extremely sensitive temperature measurements can be achieved using a heterodyne technique which beats the reflected signal against the source, similar to a Doppler radar system.

Another suitable method for sensing and monitoring temperature is to use a disposable lens with a grating to do a Hartman sensor for measuring wavefront phase. An example of such a method and apparatus is found in U.S. Patent No. 4,737,621, incorporated herein by reference. In this apparatus, the wavefront is divided into a plurality of subapertures, light is intensified and then

imaged as spots of light from each subaperture onto a detector array. The individual detector elements of the array form a plurality of electrical signals proportional to the local divergence of the vector gradient field. After reconstruction or interfacing, this gradient signal is applied to corrective mirrors which may be of the deformable or membrane type.

Another suitable optical system is disclosed in U.S. Patent No. 4,865,454, incorporated herein by reference. An adaptive optical system is provided with local wavefront sensing and control. Interferometry is used to determine wavefront phase aberration in an incoming electromagnetic beam and the reflective surface of a deformable mirror is adjusted. The apparatus synchronously detects phase differences between an interferometrically modulated beam and a uniform modulator. Since the refractive index varies with temperature and affects the wavefront of the reflected beam, wavefront measurement provides a metric for temperature measurement. In addition, changes in the cellular structure in response to treatment, such as simple thermal expansion, or emission of chemicals in response to treatment, will also initiate changes in the reflected wavefront which can then be measured and associated with the temperature rise.

The optical path through the ocular fluid is ~20mm, giving very large signal attenuation. However, modern high-end sensors can detect very low light levels simply by integrating or "photon counting", Therefore, an IR CCD thermal imager with appropriate visible filtering can be used to detect temperature elevation during TTT in much the same manner as thermal imagers are used in these other areas of medicine:

Other suitable methods and apparatus include the use of pyrometers. A suitable pyrometer is commercially available.

These disease states include but are not limited to cancer, ocular neovascularization and abnormal vascular conditions throughout the human body. Long-pulse laser photocoagulation includes but is not limited to TTT, a combination of long-pulse laser photocoagulation with at least one of PDT,

exogenous chromophores or thermally activated drugs.

In summary, the present invention provides a method and apparatus that combines thermal therapy with PDT, or thermally activated molecules or compounds, or conventional laser photocoagulation for the treatment of abnormal blood vessels that develop in the body that may be caused by tumors, eye disorders, vascular disorders, and the like. When thermal therapy is combined with PDT, the apparatus delivers optical energy at a wavelength suitable for thermal therapy, plus a second wavelength suitable for PDT. Optionally, one or more aiming wavelengths for directing the therapeutic laser(s) to the desired target may be necessary. The wavelength used for thermal therapy may be the same wavelength used for PDT. When thermal therapy is combined with conventional laser photocoagulation, the apparatus delivers optical energy at a wavelength suitable for thermal therapy, plus a second wavelength suitable for conventional laser photocoagulation. Optionally, one or more aiming wavelengths for directing the therapeutic laser(s) to the desired target may be necessary. The wavelength used for thermal therapy may be the same wavelength used for conventional short-pulse photocoagulation.

The foregoing descriptions of various embodiments of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Obviously, many modifications and variations will be apparent to practitioners skilled in this art.

CLAIMS

1. A method of creating a therapeutic change in a retinal tissue site, comprising:

controllably delivering a first treatment modality to the retinal tissue site; and

controlling delivering a second treatment modality to the retinal tissue site.

2. The method of claim 1, wherein the first treatment modality is a therapeutic or neuroprotective thermal treatment modality.

3. The method of claim 1, wherein the first treatment modality is long-pulse laser photocoagulation energy.

4. The method of claim 3, wherein the second treatment modality is photodynamic therapy.

5. The method of claim 2, wherein the second treatment modality is an exogenous chromophore modality.

6. The method of claim 2, wherein the second treatment modality is a thermally activated molecule or compound modality.

7. The method of claim 2, wherein the second treatment modality is conventional short-pulse laser photocoagulation.

8. The method of claim 2, wherein the second treatment modality is long-pulse laser photocoagulation.

9. The method of claim 1, wherein the first modality is delivered prior to delivery of the second modality.

10. The method of claim 1, wherein the second modality is delivered prior to delivery of the first modality.

11. The method of claim 1, wherein at least a portion of the first modality is delivered simultaneously with the second modality.

12. The method of claim 1, wherein the first modality is delivered simultaneously with the second modality.

13. The method of claim 1, further comprising:

controllably delivering the first and second modalities to a retinal treatment site.

14. The method of claim 13, wherein at least one predictive measurement is used to controllably deliver the first and modalities to the retinal treatment site.

15. The method of claim 14, wherein the predictive measurement is a prior measurement of a tissue response to the delivery of energy to the selected tissue site.

16. The method of claim 14, wherein the predictive measurement is a measurement of retinal reflectivity at or near a wavelength of the first dosage of energy delivered at an attenuated, subtherapeutic power that is compared with retinal reflectively values obtained from other patients' eyes.

17. The method of claim 14, wherein the predictive measurement is a measurement of optical transmission through the eye at a wavelength of the second dosage of electromagnetic energy.

18. The method of claim 17, where a light-sensing episcleral probe is

used to measure optical transmission through the eye at a wavelength of the second dosage of electromagnetic energy.

19. The method of claim 18, wherein the light-sensing episcleral probe is positioned directly posterior to a tissue site of the second dosage of electromagnetic energy.

20. The method of claim 14, wherein the predictive measurement is an application of at least one suprathreshold laser test burn at the selected tissue site.

21. The method of claim 13, wherein at least one real time measurement is used to controllably deliver to the selected tissue site.

22. The method of claim 21, wherein the real time measurement directly monitors a temperature of the selected tissue site.

23. The method of claim 21, wherein the real time measurement measures a secondary response related to temperature of the selected tissue site.

24. The method of claim 21, wherein an episcleral thermosensitive probe is used to make the real time measurement .

25. The method of claim 21, wherein transpupillary IR thermography is used to make the real time measurement.

26. The method of claim 21, wherein liposome encapsulated fluorophores are used to make the real time measurement.

27. The method of claim 21, wherein MRI is used to make the real time measurement.

28. The method of claim 21, wherein ultrasound is used to make the real time measurement.

29. The method of claim 21, wherein retinal reflectometry is used for the real time measurement.

30. The method of claim 21, wherein a thermally modulated fluorescent substance is used for the real time measurement.

31. The method of claim 21, wherein focal or multifocal ERG is used for the real time measurement.

32. The method of claim 21, wherein thermal imaging is used for the real time measurement.

33. The method of claim 21, wherein optical coherence tomography is used for the real time measurement.

34. The method of claim 21, wherein multispectral imaging is used for the real time measurement.

35. The method of claim 21, wherein fluorescent and/or autofluorescent signals are used for the real time measurement.

36. The method of claim 21, wherein retinal thickness changes as measured are used for the real time measurement..

37. The method of claim 1, further comprising:

making a measurement of the selected site to determine treatment results following delivery of the first dosage of energy.

38. A treatment system:

a first treatment modality source;

a second treatment modality source;

a tissue feedback control system coupled to at least one of the first and second treatment modality sources that provides an adjustment of a delivery of the first or second treatment modality to an ophthalmologic tissue site in response to feedback received from the ophthalmologic tissue site.

39. The system of claim 38, wherein the tissue feedback control system allows selection and programming of delivery of the first or second treatment modalities to the selected ophthalmologic tissue site.

40. The system of claim 38, wherein the first treatment modality is a therapeutic or neuroprotective thermal treatment modality.

41. The system of claim 38, wherein the first treatment modality is long-pulse laser photocoagulation energy.

42. The system of claim 41, wherein the second treatment modality is photodynamic therapy.

43. The system of claim 40, wherein the second treatment modality is an exogenous chromophore modality.

44. The system of claim 40, wherein the second treatment modality is a thermally activated molecule or compound modality.

45. The system of claim 40, wherein the second treatment modality is conventional short-pulse laser photocoagulation.

46. The system of claim 38, wherein the tissue feedback control system provides sequential delivery of optical energy to the ophthalmologic

tissue site.

47. The system of claim 38, wherein the tissue feedback control system provides adjustment and display of individual laser operating parameters.

48. The system of claim 38, wherein the tissue feedback control system provides synchronization of electromagnetic energy delivery with a drug infusion system.

49. The system of claim 38, wherein the tissue feedback control system measures power delivered from thermal and PDT energy sources to the ophthalmologic tissue site.

50. The system of claim 49, wherein the tissue feedback control system adjusts power output of thermal and PDT energy sources to obtain a desired therapeutic result at the ophthalmologic tissue site.

51. The system of claim 38, wherein the first treatment modality source is a thermal energy source and the second treatment modality source is a PDT energy source.

52. The system of claim 51, further comprising:

an energy delivery device with an optical fiber coupled to the PDT and thermal energy sources.

53. The system of claim 52, wherein the energy delivery device includes a bare fiber

54. The system of claim 52, wherein the energy delivery device includes a handpiece.

55. The system of claim 52, wherein the energy delivery device includes an EndoProbe.

56. The system of claim 52, wherein the energy delivery device includes an endoscope.

57. The system of claim 52, wherein the energy delivery device includes a slit lamp.

58. The system of claim 52, wherein the energy delivery device includes an indirect ophthalmoscope.

59. The system of claim 52, wherein the energy delivery device includes an operating microscope.

60. The system of claim 52, wherein the energy delivery device includes a laser beam scanner.

61. The system of claim 52, wherein the thermal energy source is a TTT energy source.

62. The system of claim 52, wherein

wherein the thermal energy source is a long-pulse laser photocoagulation energy source.

63. A method of treating age-related macular degeneration, comprising:

controllably delivering a first treatment modality to a retinal tissue site; and

controlling delivering a second treatment modality to the retinal tissue

site.

64. The method of claim 63, wherein the first treatment modality is a therapeutic or neuroprotective thermal treatment modality.

65. The method of claim 63, wherein the first treatment modality is long-pulse laser photocoagulation energy.

66. The method of claim 65, wherein the second treatment modality is photodynamic therapy.

67. The method of claim 64, wherein the second treatment modality is an exogenous chromophore modality.

68. The method of claim 64, wherein the second treatment modality is a thermally activated molecule or compound modality.

69. The method of claim 63, wherein the first modality is delivered prior to delivery of the second modality.

70. The method of claim 63, wherein the second modality is delivered prior to delivery of the first modality.

71. The method of claim 63, wherein at least a portion of the first modality is delivered simultaneously with the second modality.

72. The method of claim 63, wherein the first modality is delivered simultaneously with the second modality.

73. The method of claim 63, wherein the first modality is

74. The method of claim 63, further comprising:

titratively delivering the first and second modalities to the retinal treatment site.

75. The method of claim 74, wherein at least one predictive measurement is used to titratively deliver the first and modalities to the retinal treatment site.

76. The method of claim 75, wherein the predictive measurement is a prior measurement of a tissue response to the delivery of electromagnetic energy to the selected tissue site.

77. The method of claim 75, wherein the predictive measurement is a measurement of retinal reflectivity at or near a wavelength of the first dosage of energy delivered at an attenuated, subtherapeutic power that is compared with retinal reflectively values obtained from other patients' eyes.

78. The method of claim 75, wherein the predictive measurement is a measurement of optical transmission through the eye at a wavelength of the second dosage of electromagnetic energy.

79. The method of claim 78, where a light-sensing episcleral probe is used to measure optical transmission through the eye at a wavelength of the second dosage of electromagnetic energy.

80. The method of claim 79, wherein the light-sensing episcleral probe is positioned directly posterior to a tissue site of the second dosage of electromagnetic energy.

81. The method of claim 75, wherein the predictive measurement is an application of at least one suprathreshold laser test burn at the selected tissue

site.

82. The method of claim 74, wherein at least one real time measurement is used to titratively deliver to the selected tissue site.

83. The method of claim 82, wherein the real time measurement directly monitors a temperature of the selected tissue site.

84. The method of claim 82, wherein the real time measurement measures a secondary response related to temperature of the selected tissue site.

85. The method of claim 82, wherein a episcleral thermosensitive probe is used to make the real time measurement .

86. The method of claim 82, wherein transpupillary IR thermography is used to make the real time measurement.

87. The method of claim 82, wherein liposome encapsulated fluorophores are used to make the real time measurement.

88. The method of claim 82, wherein MRI is used to make the real time measurement.

89. The method of claim 82, wherein ultrasound is used to make the real time measurement.

90. The method of claim 82, wherein retinal reflectometry is used for the real time measurement.

91. The method of claim 82, wherein a thermally modulated fluorescent substance is used for the real time measurement.

92. The method of claim 82, wherein focal or multifocal ERG is used for the real time measurement.

93. The method of claim 82, wherein thermal imaging is used for the real time measurement.

94. The method of claim 82, wherein optical coherence tomography is used for the real time measurement.

95. The method of claim 82, wherein multispectral imaging is used for the real time measurement.

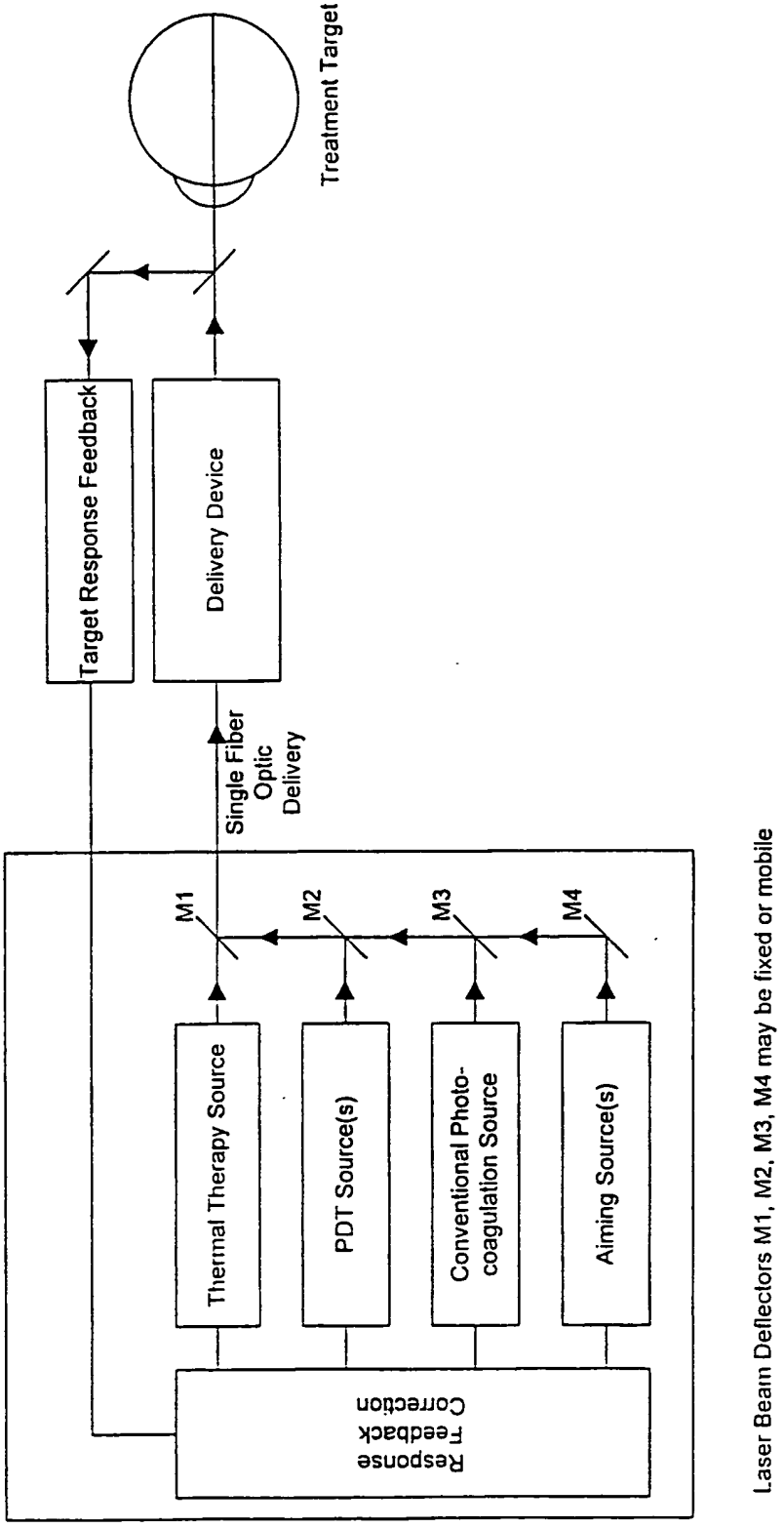
96. The method of claim 82, wherein fluorescent and autofluorescent signals are used for the real time measurement.

97. The method of claim 82, wherein retinal thickness changes as measured are used for the real time measurement..

98. The method of claim 63, further comprising:

making a measurement of the selected site to determine treatment

Figure 1


Treatment Target
Target Response Feedback
Delivery Device
Single Fiber Optic Delivery
M1
M2
M3
M4
Thermal Therapy Source
PDT Source(s)
Conventional Photo-coagulation Source
Aiming Source(s)
Response Feedback Correction
Laser Beam Deflectors M1, M2, M3, M4 may be fixed or mobile

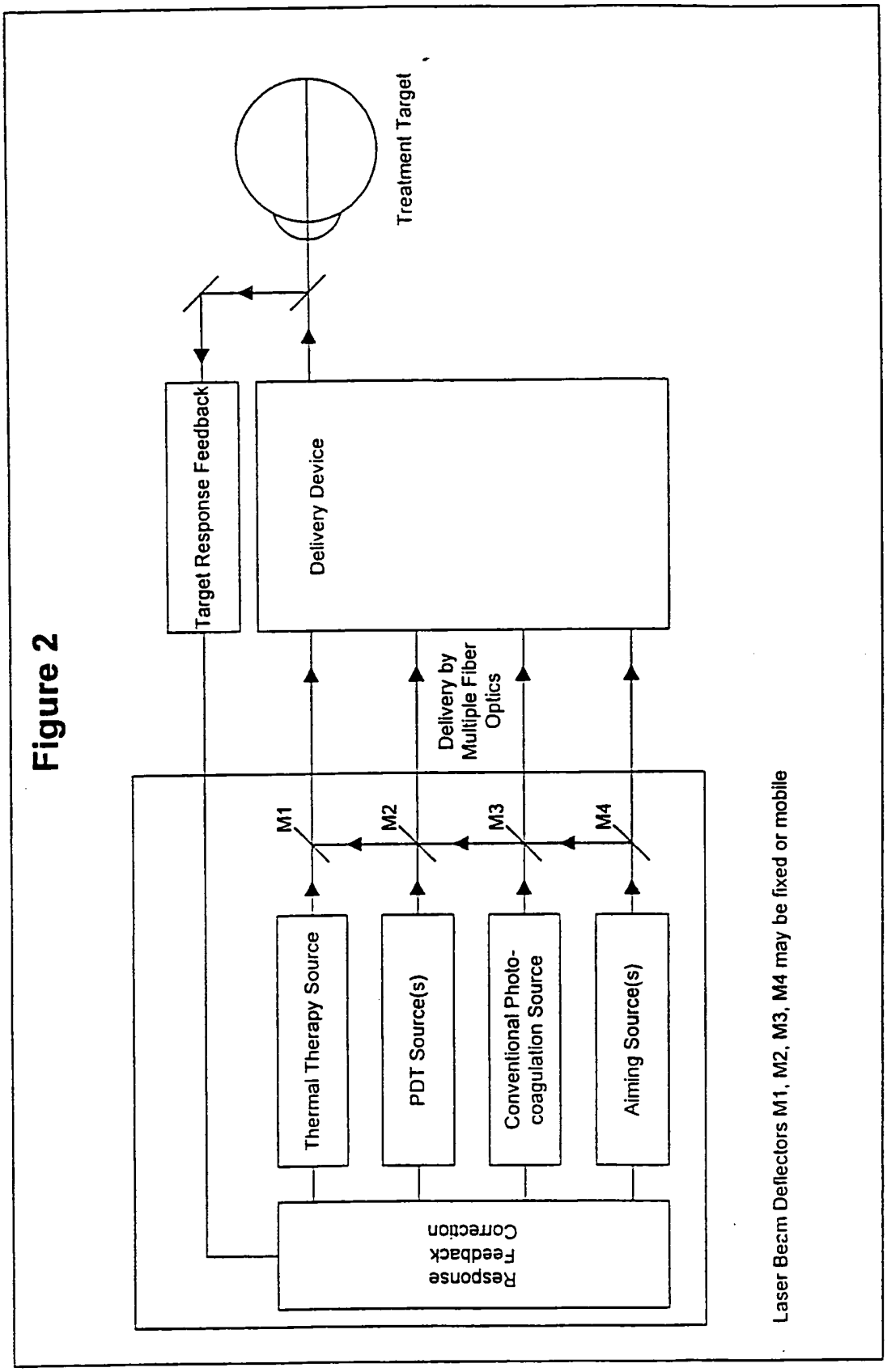

Treatment Target
Target Response Feedback
Delivery Device
Delivery by Multiple Fiber Optics
M1
M2
M3
M4
Thermal Therapy Source
PDT Source(s)
Conventional Photo-coagulation Source
Aiming Source(s)
Response Feedback Correction
Laser Beam Deflectors M1, M2, M3, M4 may be fixed or mobile

Figure 2

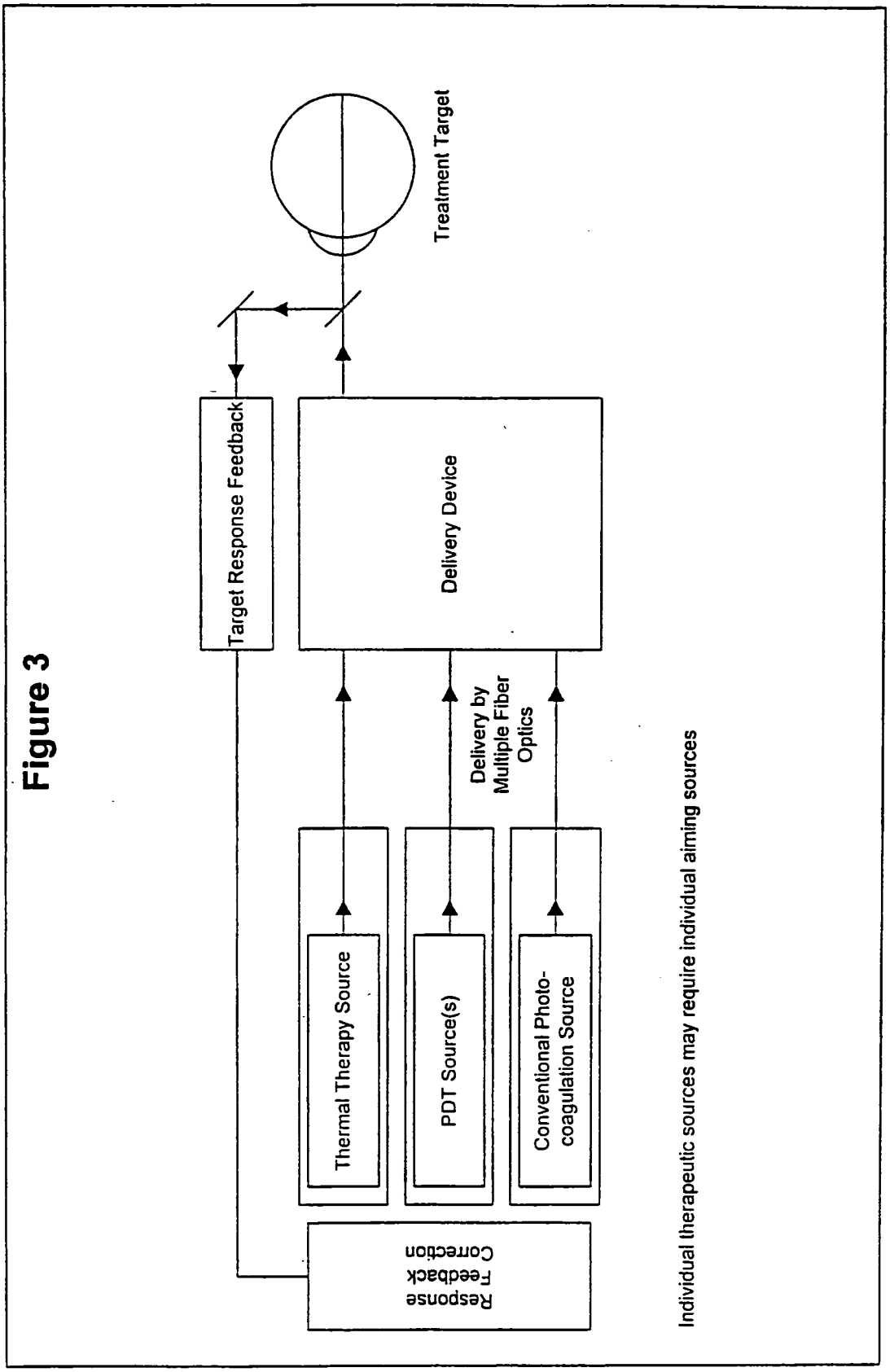

Treatment Target
Target Response Feedback
Delivery Device
Delivery by Multiple Fiber Optics
Thermal Therapy Source
PDT Source(s)
Conventional Photo-coagulation Source
Response Feedback Correction
Individual therapeutic sources may require individual aiming sources

Figure 3

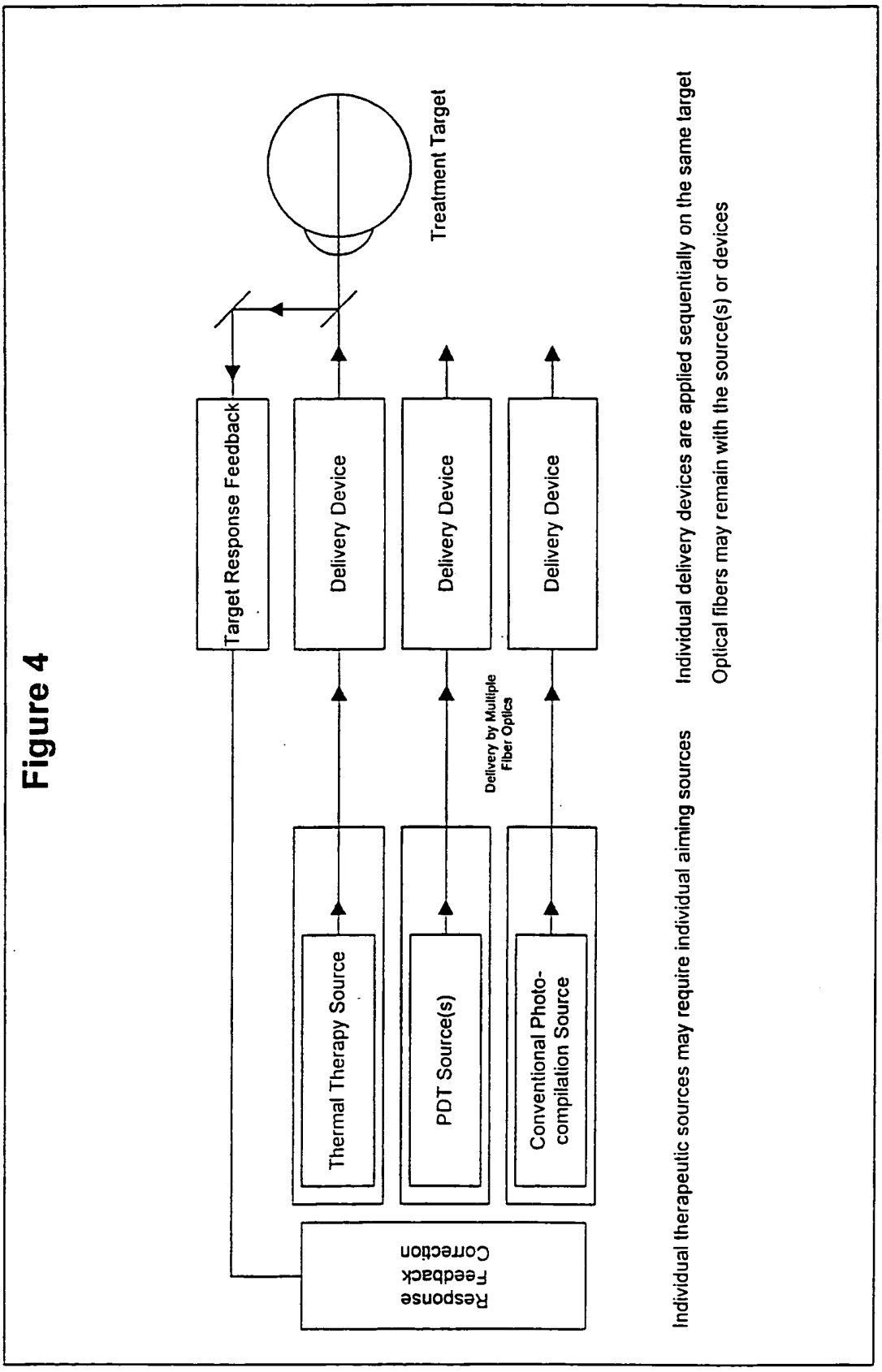

Treatment Target
Target Response Feedback
Delivery Device
Delivery Device
Delivery Device
Delivery by Multiple Fiber Optics
Thermal Therapy Source
PDT Source(s)
Conventional Photo-compilation Source
Response Feedback Correction
Individual therapeutic sources may require individual aiming sources
Individual delivery devices are applied sequentially on the same target
Optical fibers may remain with the source(s) or devices

Figure 4

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 00/28446

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F9/008

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	US 5 892 569 A (VAN DE VELDE FRANS J) 6 April 1999 (1999-04-06) column 4, line 5 - line 6 column 9, line 27 - line 30 column 9, line 67 -column 10, line 21	38-47, 49-51 52
Y	US 5 423 801 A (MARSHALL JOHN ET AL) 13 June 1995 (1995-06-13) column 11, line 4 - line 14; figure 1	38-47, 49-51
A	WO 93 21842 A (QUADRA LOGIC TECH INC ;AMERICAN CYANAMID CO (US)) 11 November 1993 (1993-11-11) page 15, line 29 -page 16, line 2; figure 4	38

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	09/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mayer, E

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INTERNATIONAL SEARCH REPORT

Interr ›nal Application No
PCT/US 00/28446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 933 096 A (IBM) 4 August 1999 (1999-08-04) column 19, line 46 - line 52	38

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...ormation on patent family members

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